LAUNCHPAD REPORT

NEUROLOGICAL AND NEUROPSYCHIATRIC DISEASES WORKING GROUP

MEMBERS OF THE WORKING GROUP:

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DISEASE / DISEASE AREA UNDER CONSIDERATION:

- Frontotemporal Dementia

Rapporteurs

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The reports will serve as the basis for discussion at the Disease Workshop in Paris on October 16-17th.

Please provide as many numbers and information as possible to ensure that the most appropriate diseases for the LifeTime context can be identified.

If possible, use numbers for Europe and take into account potential differences between countries. If you use a specific country (or more), please indicate. In case of considerable variation between countries, please provide highest/lowest number additionally to the aggregated data (eg. data for the EU plus data for the countries at both ends of the scale).

If available, please include data by sex and, if important in the context of the disease, by age.

The given examples from selected diseases or disease areas are an indication of how the questions could be answered, please provide additional or other data if you feel that they are more significant for the disease.

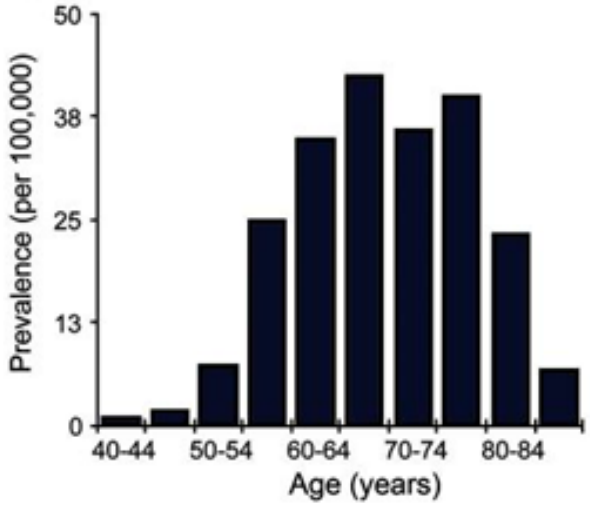
DISEASE SELECTION CRITERIA

a. SOCIETAL IMPACT

i) Incidence and Prevalence

The most recent figures for incidence and prevalence in Europe come from a UK study which reports:

- A European-standardized point prevalence (with 95% confidence intervals) of 10.84 (9.27-12.42) /100,000; for men 10.93 (8.66-13.20) /100,000; for women 10.76 (8.57-12.95) /100,000. Prevalence at different ages is shown in the figure below (taken from the study). This estimate is generally in line with previous studies. One older study from the UK reported that the prevalences of early-onset FTD and AD were the same: 15 per 100,000 (8.4 to 27.0) in the 45- to 64-year-old population.



- A standardized incidence of 1.61 (1.14-1.99) /100,000 person-years. The lifetime risk (standardized for age and sex) was found to be 1 in 742.

Sources:
Coyle-Gilchrist et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology. 2016 May 3;86(18):1736-43.
Ratnavalli et al. The prevalence of frontotemporal dementia. Neurology. 2002 Jun 11;58(11):1615-21.

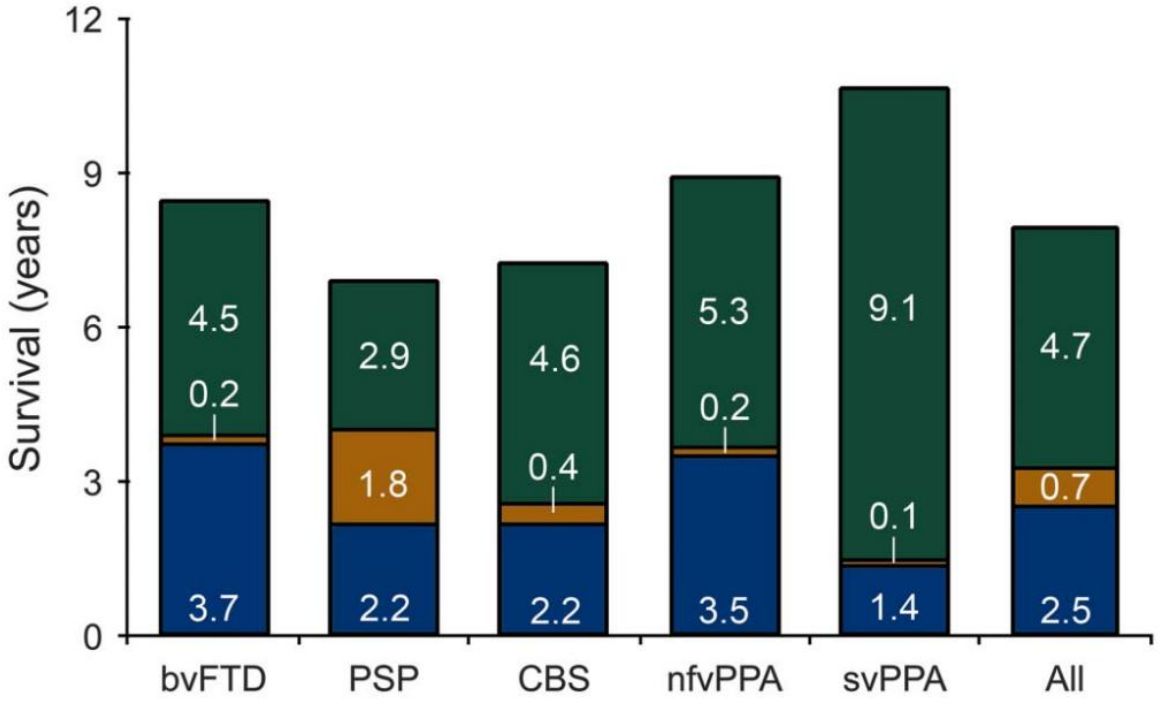
ii) Disease severity

Mortality
Age-adjusted all cause mortality is 1.57 (1.15-1.99) /100,000 person-years. It has been estimated that this would remain unchanged moving forward into the future.

Source: Coyle-Gilchrist et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology. 2016 May 3;86(18):1736-43.

Survival after diagnosis

Given its midlife onset, FTD causes a dramatic reduction in life expectancy. Studies of FTD survival are difficult to conduct due to the important heterogeneity of clinical manifestations (see below). There is no evidence that survival is associated with the demographic characteristics of individuals with FTD, the age at disease onset or the severity of dementia at the time of diagnosis. The graph below shows that survival differs for the different clinical syndromes within FTD. Blue here is time to diagnosis of a degenerative disorder, brown to a specific diagnosis, and green to death.



bvFTD = behavioral variant frontotemporal dementia; PSP = progressive supranuclear palsy; CBS = corticobasal syndrome; nfvPPA = nonfluent variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia.

Sources:

Coyle-Gilchrist et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology. 2016 May 3;86(18):1736-43.

Onyike et al. The Epidemiology of Frontotemporal Dementia. Int Rev Psychiatry. 2013 April;25(2): 130–137.

Potential years of life lost

No specific analysis of YLLs has been performed in FTD, but potential years of life lost because of dementia in people aged 75 years or older has been estimated at 3–5 years; with a younger onset in FTD the potential years of life lost would be expected to be much greater than this.

iii) Economic impact

Little work has been performed to investigate the economic impact of FTD. However, one key study run by a patient advocacy group (the Association for Frontotemporal Degeneration) provides

important data and shows that there is a significant economic impact from FTD in the affected families. In fact, a comparison to Alzheimer's disease (AD) revealed that the economic costs of Alzheimer's disease (AD) were 53% lower than the costs of FTD. Much of this difference can be attributed to loss of productivity due to the younger age of onset in FTD pulling both patient and caregiver out of the workforce at a time where they are likely to be at the height of their careers. Also, two out of three FTD caregivers reported a notable decline in their own health, and more than half said that they had incurred increased personal health costs. Specifically the study found:

Change in household income and lost days of work
There is a decline in household income after diagnosis: A median loss of 7.0 days of work per 4 weeks was reported within a household (see table below).

		FTD subtype			
	Total	bvFTD	PPA	FTD-MND	PSP/CBS
12 mo before DX, $	75,000-99,999	75,000-99,999	75,000-99,999	60,000-74,999	50,000-59,999
12 mo after DX, $	50,000-59,999	50,000-59,999	50,000-59,999	35,000-49,999	40,000-49,999
p Value	<0.001	<0.001	<0.001	0.001	0.003
	Type of caregiver			Patient sex	
	Spouse CG	Child CG	Other CG	Male	Female
12 mo before DX, $	75,000-99,999	40,000-49,999	75,000-99,999	75,000-99,999	75,000-99,999
12 mo after DX, $	50,000-59,999	30,000-34,999	35,000-39,999	50,000-59,999	40,000-49,999
p Value	<0.001	0.001	<0.001	<0.001	<0.001

Abbreviations: bvFTD = behavioral variant of frontotemporal degeneration; CG = caregiver; DX = diagnosis; FTD-MND = frontotemporal degeneration with motor neuron disease; PPA = primary progressive aphasia; PSP/CBS = progressive supranuclear palsy/corticobasal syndrome.
Median ranges.

Estimates of annual per patient costs
Galvin et al estimate the following costs (converted to Euros):

- Direct i.e. the value of goods and services for which there are explicit monetary payments: 43,500 Euros
- Indirect i.e. the value of the changes in the provision of goods and services that are attributable to FTD but for which there are no explicit monetary payments: 65,200 Euros

Source: Galvin et al. The social and economic burden of frontotemporal degeneration. Neurology. 2017, 89(20), 2049-2056.

iv) Pressing need for new and more efficient clinical treatment

There are no curative treatments for FTD at present and so there is an absolutely pressing need to develop new therapies, both from a disease-modifying perspective and from a symptomatic point of view.

Management is currently only directed at controlling symptoms, and helping patients and their carers cope with the impact of the illness. Non-pharmacological management strategies are based largely on anecdotes and clinical experience rather than controlled evidence, whilst options for pharmacotherapy are limited:

"The available evidence [for symptomatic therapies in FTD] is derived largely from small, open label studies or case reports. Open label studies have shown no clear symptomatic benefit for cholinesterase inhibitors or memantine, and one randomised, double blind trial of memantine in behavioural variant FTD was also negative; these agents may aggravate behavioural disturbance. Small, double blind, controlled trials have provided some evidence for modest improvement of behavioural symptoms with trazodone though not paroxetine. Clinical experience suggests that selective serotonin reuptake inhibitors may be useful in modulating intrusive or compulsive behaviours in some patients. Neuroleptic drugs are potentially associated with substantial risk of extrapyramidal and cognitive side effects,but adequate controlled studies to estimate the risk-benefit balance of these agents in FTD are lacking. For the moment, it seems pragmatic to reserve use of neuroleptics to newer generation agents at low doses when required for agitation that threatens the patient's wellbeing and cannot be managed by other means. Limited data from a single randomised controlled trial suggest a transient benefit of intranasal oxytocin on emotion processing in behavioural variant FTD."

Source: Warren, Rohrer and Rossor. Clinical review. Frontotemporal dementia. BMJ. 2013, 347:f4827.

v) Strong need for early diagnosis

EARLY SCREENING TESTS/TECHNOLOGIES AVAILABLE

No X

Lack of early and accurate diagnosis in FTD

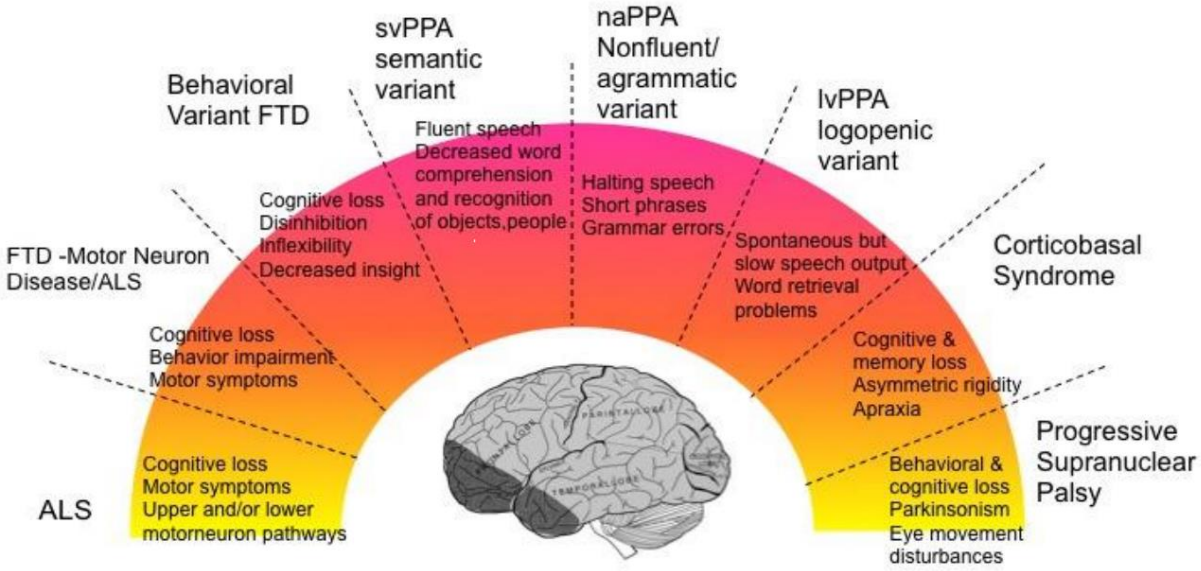
Within the wide range of neurodegenerative brain diseases, the differential diagnosis of FTD frequently poses a challenge. In large part this is a consequence of the wide variability in clinical presentations that can be associated with FTD, and the frequent occurrence of atypical presentations which may mimic other dementias, most commonly AD. Indeed, both false positive and false-negative diagnoses are most often confounded with AD.

Source: Harris et al. Sensitivity and specificity of FTDC criteria for behavioral variant frontotemporal dementia. Neurology. 2013 May 14;80(20):1881-7.

Moreover, FTD often affects individuals younger than 65 years of age, and symptoms in this younger age population are often mistaken for psychiatric disorders, causing a delay in correct diagnosis. An Australian Study 'Improving Service for Younger Onset Dementia (INSPIRED)' found an average 4.7 years from symptom onset to final diagnosis, with an earlier age at onset and the presence of depression (prevalent in FTD) as important factors leading to longer times to diagnosis. Together, the lack of an early and accurate diagnosis leads to frequent misdiagnosis and an underestimation of the true number of FTD patients.

Sources:
Gossye et al. The Use of Biomarkers and Genetic Screening to Diagnose Frontotemporal Dementia: Evidence and Clinical Implications. Front Neurosci. 2019, 13:757.
Draper et al. Time to diagnosis in young-onset dementia and its determinants: the INSPIRED study. Int J Geriatr Psychiatry. 2016, 31(11):1217-1224.

By definition, FTD patients are neuropathologically characterized by the relatively localized degeneration of the frontal and anterior temporal lobes (also called frontotemporal lobar degeneration). The clinical presentations resulting from neurodegeneration in these brain areas are diverse (see figure below), with some patients presenting with progressive changes in behaviour (behavioural variant FTD, bvFTD) while others have language dysfunction presenting as primary progressive aphasia (PPA). A combination of these symptoms is also common and additional symptomatic overlap with atypical parkinsonian disorders such as progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) or motor neuron disease (MND) exists.

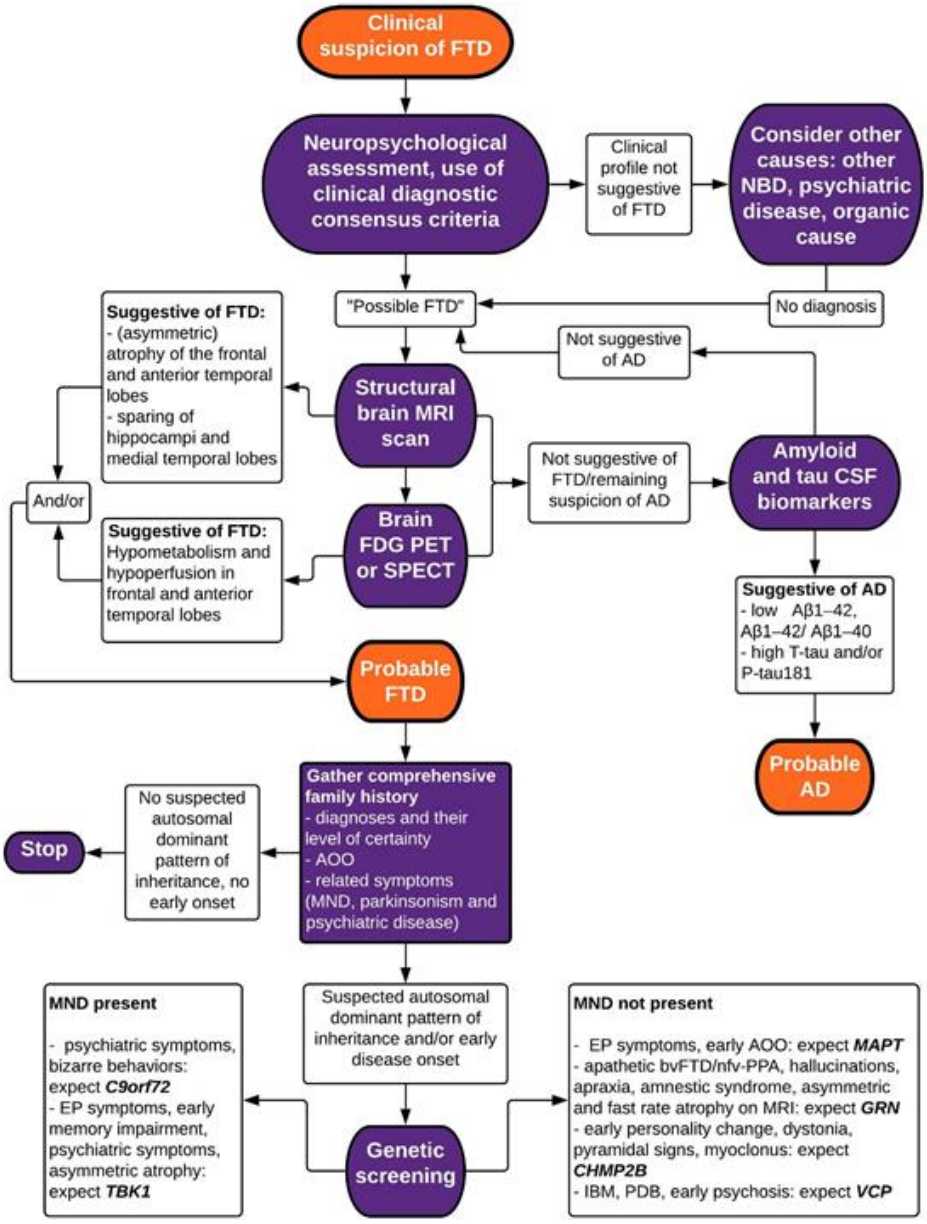


Source: Nadine Tatton for the Association for Frontotemporal Dementia - FTD Research and Drug Development Landscape - available at https://www.theaftd.org/wp-content/uploads/2014/05/FTD-Research-and-Drug-Development-Landscape.pdf

What adds to the complexity is the fact that pathological lesions composed of inclusions with various compositions of disease proteins are found to accumulate in these affected brain areas. Tau and TDP-43 proteinopathies are the most common pathological subtypes, whereas a third pathological subtype, FTD with FUS pathology, comprises about 10% of patients. There is no clear link between the clinical presentation and a given protein pathology in the majority of cases. This means that when a patient comes to an FTD clinic, even experienced clinicians do not know if they are dealing with an underlying tau, TDP-43, or FUS pathology. It also means that a therapy trial cohort enrolled by way of clinical and imaging criteria but without a biomarker that ascertains an underlying molecular pathology, might constitute a mix of people with tau, TDP-43, or FUS pathology. This may be workable for neuroprotective or other drugs that target common mechanisms of neurodegeneration, but for drugs that specifically target tau or TDP-43, it would significantly dilute the number of people in the cohort who are likeliest to respond to the therapy.

The clinical diagnosis of bvFTD and the language variants of FTD are based on clinical diagnostic consensus criteria. These criteria are based on the presenting core symptoms complemented with results from imaging modalities including magnetic resonance imaging (MRI), 18-fluorodeoxglucose (FDG) positron emission tomography (PET) scans, single-photon emission tomography (SPECT) scans

and DNA screening for causal mutations (See Figure below from Gossye et al. PMID: 31447625). For bvFTD these criteria reach 85-95% sensitivity and 82% specificity to identify possible FTD, and 75-85% and 95% sensitivity and specificity for probably bvFTD. There are no routinely used and validated specific CSF or blood biomarkers for the diagnostics of FTD. Some patients are tested for CSF levels of Ab1-42 levels, Ab1-42/ Ab1-40 ratio, total tau and phospho-tau levels - not to aid in the diagnosis of FTD - but rather to make a diagnosis of underlying Alzheimer's pathology, which can be seen in some patients presenting with an FTD phenotype. One promising new biomarker for FTD which is currently studied in a research setting is Neurofilament Light Protein (NfL). Neurofilaments are structural axonal proteins and their presence in biofluids is a marker of neurodegeneration. A systematic review and meta-analysis of European research studies found that CSF NfL has potential to assist in the differentiation of FTD from AD.



Sources:

Rascovsky and Grossman. Clinical diagnostic criteria and classification controversies in frontotemporal lobar degeneration. Int Rev Psychiatry. 2013 Apr;25(2):145-58.

Gorno-Tempini et al. Classification of primary progressive aphasia and its variants.Neurology. 2011 Mar 15;76(11):1006-14. PMID: 21325651
Bridel et al. Diagnostic Value of Cerebrospinal Fluid Neurofilament Light Protein in Neurology: A Systematic Review and Meta-analysis. JAMA Neurol. 2019 Jun 17. doi: 10.1001/jamaneurol.2019.1534.

Potential benefits of early FTD diagnosis

Personal and social perspective: A survey among dementia caregivers from 5 European countries found that 53% of respondents indicated that an earlier diagnosis would have been desirable. Especially in FTD, where behavioural and psychiatric changes are common, an earlier diagnosis could reduce the burden and stress on the families by providing much needed informational context to the changes observed in their loved ones. Even without the availability of effective treatment options, it will allow the family to plan ahead, and to benefit from symptomatic treatments and social services.

Source: Woods et al. Timely diagnosis of dementia? Family carers' experiences in 5 European countries. Int J Geriatr Psychiatry. 2019, 34(1):114-121.

From therapeutic development perspective: As discussed there are no routinely used and validated specific CSF or blood biomarkers for the diagnostics of FTD. However, there is an urgent need for such biomarkers for differential diagnostics, disease monitoring, and assessment of the effects of potential therapeutic treatments in FTD patients. Biomarkers which could aid in an early diagnosis - showing specific changes already at the presymptomatic or prodromal phase of the disease - would be especially valuable for disease prediction and intervention when pharmacological, lifestyle, or psychosocial interventions become available. There thus is a need for novel biomarkers that are correlated with the earliest biochemical and cellular changes in the brain, well before the start of clinical symptoms. Cell and fluid biomarkers, which might be identified based on pathways unravelled by single-cell studies, will be essential to identify and stratify patients into distinct patient groups which could benefit from specific disease modifying treatments (e.g. tau versus TDP-43 based treatments).

b. HETEROGENEITY ON THE CELLULAR LEVEL THAT NEEDS TO BE DECIPHERED FOR DISRUPTIVE CLINICAL AVENUES

Multiple functional pathways and cell types are disrupted in FTD

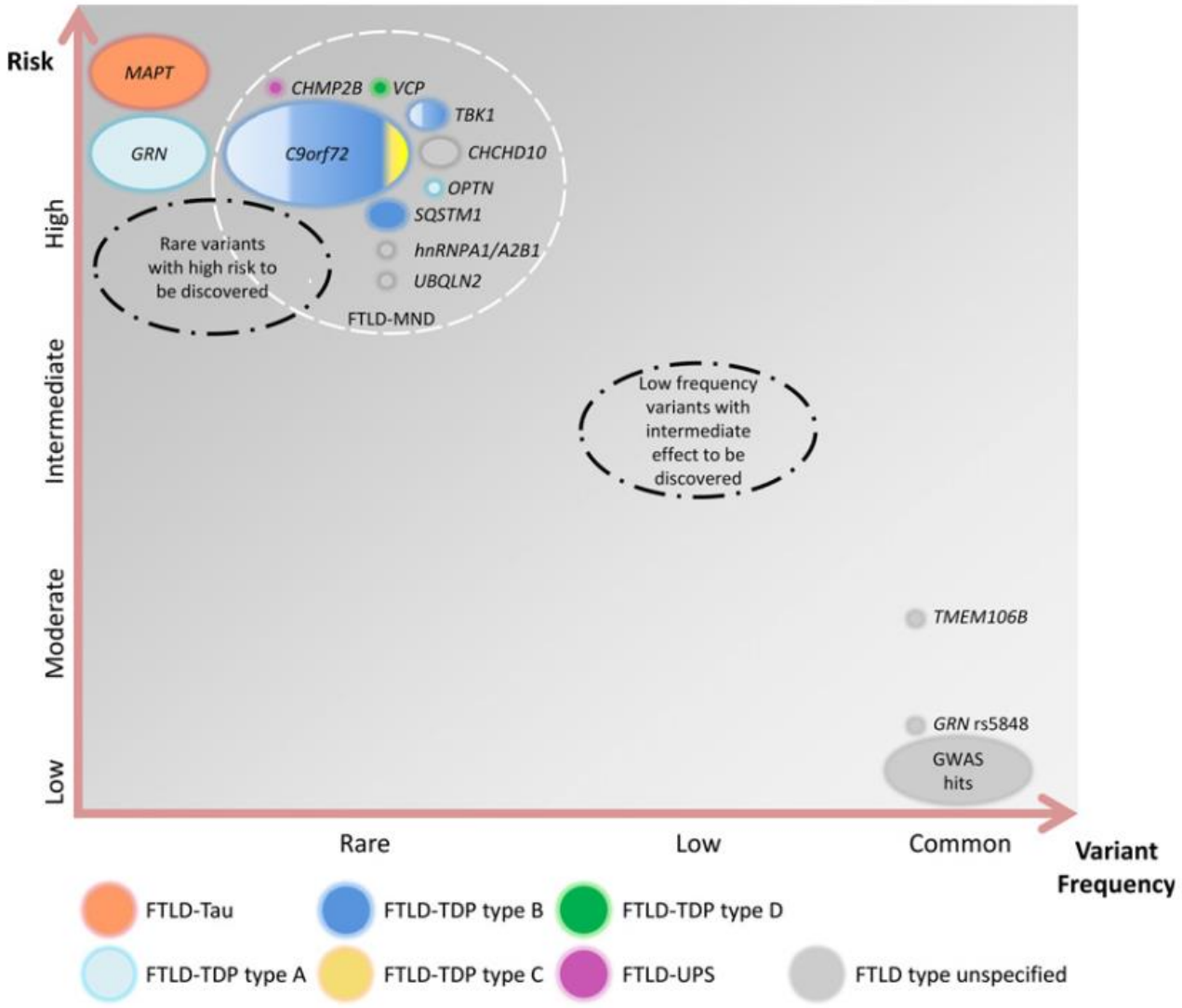
As described in the previous sections, FTD encompasses a highly heterogeneous group of disorders both in terms of clinical presentations and neuropathology. FTD is also heterogeneous at the genetic and molecular level with evidence of disruptions in multiple functional pathways. A comprehensive understanding of this heterogeneity at the cellular level will be crucial for future successful disease therapies.

Significant insight into the pathological mechanisms underlying FTD have come from genetic studies. Approximately 43% of FTD patients have a positive family history [at least one affected first-degree family member with dementia, ALS, or PD] Wood et al. 2013) and between 10.2% and 27% of FTD patients have an autosomal dominant presentation of the disease. The broad definition of a family history of FTD which includes relatives affected by other neurodegenerative diseases is typical for

FTD and a direct consequence of the significant clinical variability associated with this disorder, even within single families.

Sources:
Goldman et al. Comparison of family histories in FTLD subtypes and related tauopathies. Neurology. 2005 Dec 13;65(11):1817-9.
Ratnavalli et al. The prevalence of frontotemporal dementia. Neurology. 2002 Jun 11;58(11):1615-21.
Rascovsky et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011, 134(Pt 9):2456-77.
Rohrer et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009 Nov 3;73(18):1451-6.
Rosso et al. Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. Brain. 2003, 126(Pt 9):2016-22.
Seelaar et al. Distinct genetic forms of frontotemporal dementia. Neurology. 2008 Oct 14;71(16):1220-6.
Wood et al. Development and Validation of Pedigree Classification Criteria for Frontotemporal Lobar Degeneration. JAMA Neurol. 2013, 70(11): 1411–1417.

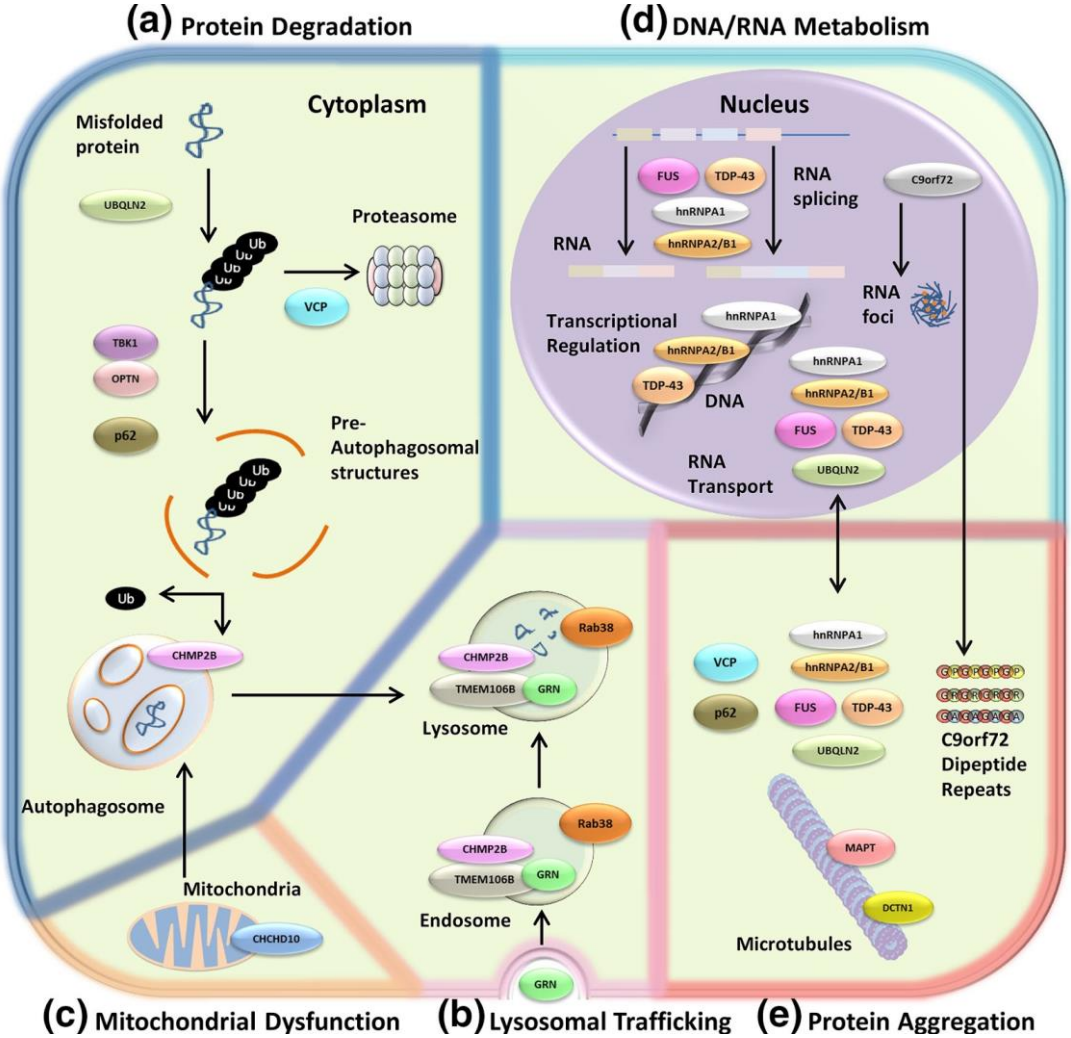
Significant successes have been made in gene identification through the study of individual FTD families with three major causal genes (mutations in microtubule associated protein tau (MAPT) and progranulin (GRN) and repeat expansions in chromosome 9 open reading frame 72 (C9orf72)) and several less common FTD disease genes identified. Genetic association studies have further identified common risk factors, either through large clinical cohorts or through the use of pathologically homogenous subpopulations of patients, as illustrated in the figure below:



Source: Pottier et al. Genetics of FTLD: overview and what else we can expect from genetic studies. J Neurochem. 2016 Aug;138 Suppl 1:32-53.

Based on the growing number of genes and pathologies implicated in FTD, a number of disease pathways are emerging that are likely implicated in FTD (see figure below from Pottier et al. 2016). A first pathway clusters around the degradation and clearance of aggregated proteins, in particular autophagy and proteasomal degradation, including CHMP2B, VCP, UBQLN2, SQSTM1, TBK1, and OPTN. Patients with these mutations often have FTD and amyotrophic lateral sclerosis (ALS). In contrast, most genes that lead to pure FTD are part of a second pathway involving the lysosomal/endosomal system, such as GRN and CHMP2B. TMEM106B, a key protein regulating lysosomal biology and function and the only established genetic risk and modifying factor for FTD, further support this and so does RAB38, a potential risk factor for bvFTD. A third pathway includes genes involved in RNA/DNA metabolism: TARDBP, FUS, C9orf72, TIA1, hnRNPA1, hnRNPA2/B1, and UBQLN2. Mutations in CHCHD10 suggest the potential involvement of the mitochondrial pathway in FTD. More recently, an important role for genes implicated in immunity and inflammation were

identified in FTD and unbiased genetic, transcriptomic, and proteomic surveys using human data confirmed significantly altered immune-function genes and altered transcript and protein modules associated with inflammation and immune function. Several of the other causal and FTD risk genes are also interconnected at the transcriptional and protein level. Together these studies have shown that there is heterogeneity in the molecular pathways that underlie FTD in individual patients. These findings also suggests that in addition to the crucial role of neurons in FTD, other cell types, including astrocytes, brain-resident microglia and peripheral myeloid cells are likely to contribute to the disease mechanism, and potentially at an earlier time-point in the disease course. The contribution and mechanism by which each cell type contributes to FTD will vary between patients. In that regard it was recently shown through neuropathological studies that there are differences in the microglial response is in FTD patients with GRN as compared to C9ORF72 mutations.



Sources:

Ferrari et al. Frontotemporal dementia: insights into the biological underpinnings of disease through gene co-expression network analysis. Mol Neurodegener. 2016, 11:21.

Pottier et al. Genetics of FTLD: overview and what else we can expect from genetic studies. J Neurochem. 2016, 138 Suppl 1:32-53.

Pottier et al. Genome-wide analyses as part of the international FTLD-TDP whole-genome sequencing consortium reveals novel disease risk factors and increases support for immune dysfunction in FTLD. Acta Neuropathol. 2019, 137(6):879-899.

Sakae et al. Microglia in frontotemporal lobar degeneration with progranulin or C9ORF72 mutations. Ann Clin Transl Neurol. 2019, 6(9):1782-1796.

Research opportunities and questions related to cellular heterogeneity in FTD:
Single cell gene expression studies in FTD patients have not yet been performed but are desperately needed to fully understand the pathological processes underlying FTD. Bulk RNA sequencing studies have used bioinformatics approaches to correct for the differences in cellular composition in individual patients, but subtle differences in specific cell types have surely gone undetected using these methods. Interestingly, despite these current limitations, significant evidence implicating distinct cellular effects in response to FTD risk genes have already been reported. For example, genetic variants in the FTD risk factor TMEM106B were shown to lead to distinct gene expression patterns in aged brains as a result of changes in cell-type composition. These same TMEM106B risk variants were found to be the most powerful genetic variants to predict neuronal proportion in cortical brain tissue samples where the cellular population structure was inferred from bulk RNA sequencing data. A deeper understanding of the effects of TMEM106B at the cellular level will be important to determine whether TMEM106B could be a potential target for neuronal protection therapies to ameliorate cognitive and functional deficits. Moreover, as we try to decipher the specific functional variants in FTD risk loci emerging from genome-wide association studies, it is expected that several risk loci will harbor non-coding variants affecting gene regulation. Many of these variants may affect epigenetic changes in a cell type specific manner (e.g. variants may be located in astrocyte specific enhancer or may only affect certain neuronal populations). Specific single cell applications such as single-nucleotide methylcytosine sequencing (snmC-seq) may offer a powerful approach to characterize the epigenomic diversity within individual neuronal cells and the changes in single cell methylomes in disease.

Sources:
Li et al. The TMEM106B FTLD-protective variant, rs1990621, is also associated with increased neuronal proportion. Acta Neuropathol. 2019 Aug 27. doi: 10.1007/s00401-019-02066-0.
Luo et al. PMID: Single-cell methylomes identify neuronal subtypes and regulatory elements in mammalian cortex. Science. 2017, 357(6351):600-604.
Ren et al. TMEM106B haplotypes have distinct gene expression patterns in aged brain. Mol Neurodegener. 2018, 13(1):35.

Another important question is to what extent changes at the cellular level contribute to the significant variability in clinical presentation that is seen in patients affected by the same mutation (e.g. C9orf72 or GRN) even within the same family. Onset ages can vary from early 30s to late 80s and clinical phenotypes may include bvFTD, PPA, FTD with ALS or even AD. For C9orf72, it has been well documented that there is somatic instability in the length of the repeat expansion in both blood and brain but clear correlations with repeat length are still lacking. More generally, the contribution of somatic mutations, affecting only a proportion of cells in relevant brain regions, to the development of FTD patients has not been studied. One particular group of patients (FTD with FUS pathology) is characterized by a relatively uniform clinical and pathological presentation but a complete lack of family history. This patient population as well as other young onset sporadic FTD patients should be studied for the presence of somatic brain mutations using emerging single cell technologies.

Sources:
Foxe et al. Intrafamilial Phenotypic Variability in the C9orf72 Gene Expansion: 2 Case Studies. Front Psychol. 2018, 9:1615.
Pottier et al. Potential genetic modifiers of disease risk and age at onset in patients with frontotemporal lobar degeneration and GRN mutations: a genome-wide association study. Lancet Neurol. 2018, 17(6):548-558.
Urwin et al. FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration. Acta Neuropathol. 2010, 120(1):33-41.
van Blitterswijk et al. Association between repeat sizes and clinical and pathological characteristics in carriers of C9ORF72 repeat expansions (Xpansize-72): a cross-sectional cohort study. Lancet Neurol. 2013, 12(10):978-88.

Unknown environmental exposures may also contribute to non-inherited forms of FTD, potentially through mutational changes at the single cell level. In the Western Pacific, the genotoxic chemical methylazoxymethanol, which is derived from seeds of the cycad plant, has been proposed as the likely cause of a cluster of patients with the so called ALS-Parkinsonian dementia complex which is characterized by tau pathology in all and additional TDP-43 pathology in some patients. It has been hypothesized that this genotoxic agent generates methyl free radicals that damage DNA leading to mutations within individual neurons. Several FTD-disease associated proteins, including FUS and TDP-43 have also been shown to be involved in the cellular DNA damage response. The availability of single cell sequencing provides an opportunity to determine whether DNA damage actually accrues in neurons as compared to glial cells in sporadic FTD patients and to what extent DNA damage, gene expression and abnormal protein deposition are linked.

Sources:
Spencer. Hypothesis: Etiologic and Molecular Mechanistic Leads for Sporadic Neurodegenerative Diseases Based on Experience With Western Pacific ALS/PDC. Front Neurol. 2019 Jul 31;10:754.
Mitra et al. Motor neuron disease-associated loss of nuclear TDP-43 is linked to DNA double-strand break repair defects. Proc Natl Acad Sci U S A. 2019 Feb 15. pii: 201818415.

AVAILABILITY OF CELL AND TISSUE SAMPLES IN BIOBANKS AND/OR OF RESPECTIVE PATIENT COHORTS

Yes X

Patient cohorts

1. **The Genetic FTD Initiative** (GENFI) is the largest cohort of participants with (or at risk of) genetic FTD with over 1000 people currently enrolled from 27 centres (23 in Europe and 4 in Canada - see figure below). Data and samples (in the GENFI biobank) are stored at University College London (PI: Rohrer) including clinical, cognitive, imaging, blood (DNA, RNA, plasma, serum) and CSF. The GENFI study collaborates with other genetic FTD cohort studies around the world through the FTD Prevention Initiative (FPI) which incorporates GENFI, the ARTFL/LEFFTDS (ALLFTD) study in the US and West Canada, and the DINAD study in Australia.

Sources:
Rohrer et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol. 2015, 14(3):253-62. [GENFI cohort]
Dopper et al. Structural and functional brain connectivity in presymptomatic familial frontotemporal dementia. Neurology. 2014, 83(2):e19-26 [Dutch RISC cohort]
Fournier et al.. Relations between C9orf72 expansion size in blood, age at onset, age at collection and transmission across generations in patients and presymptomatic carriers. Neurobiol Aging. 2019, 74:234.e1-234.e8. [French cohort]
Steinacker et al. Serum neurofilament light chain in behavioral variant frontotemporal dementia. Neurology. 2018, 91(15):e1390-e1401. [German FTLDc cohort]

2. Individual genetic FTD cohorts in Europe are largely encompassed within GENFI, with the largest being the RISC cohort in the Netherlands (van Swieten) and the French Clinical and Genetic Research Network on FTLD/FTLD-ALS (Le Ber):

- Genetic cohort of the French clinical and genetic research on FTD/FTD-ALS (17 French sites): DNA for >500 patients, >100 cell lines, >50 plasma samples with clinical data.
- The Stockholm-Sweden site is a partner of GENFI since 2012, and has enrolled 44 presymptomatic at risk individuals which has generated 113 visits including MRI, EEG, CSF, plasma, serum, DNA, RNA and fibroblasts. A total of 16 different families are enrolled out of the >70 identified families with genetic FTD. The Malmö/Lund are currently setting up the GENFI-protocol for at risk subjects.

3. There are no cross-country multicentre sporadic FTD cohorts in Europe. However individual countries have large country-wide cohorts e.g. Germany (FTLD consortium - Otto, DZNE DESCRIBE-FTD cohort - Schneider, Co-PI: Synofzik), France (French Clinical and Genetic Research Network on FTLD/FTLD-ALS - Le Ber), Sweden (Swedish FTD Initiative - Graff), Spain (CATFI - Sanchez-Valle):

- DZNE DESCRIBE-FTD (9 German sites): comprehensive longitudinal collection of clinical, cognitive, MRI, biofluid (including CSF) and cell data and samples; 374 FTD patients (8/2019) with at least baseline assessment, >300 blood samples, >100 CSF samples,
- French clinical and genetic research on FTD/FTD-ALS (17 French sites): collection of biological samples (DNA, cell lines, fibroblasts, plasma) & clinical data of >700 non-genetic FTD patients
- The Swedish FTD Initiative, a national network including all memory clinics in Sweden (8 Swedish sites) recently came together for the first time to set up common clinical routines with the aim to share samples and clinical data for research on all prospective patients with FTD/FTD-ALS. The largest sites Stockholm and Malmö/Lund have together a collection of more than >300 patients including DNA, serum, plasma and CSF as well as clinical data and MRI. PET is also available on some. There are more than 150 postmortem brain tissue donors of FTD available for research. A brain donation program is available and Stockholm provides a national clinical genetics unit for hereditary dementias. 52 whole genome sequences and 7 WES are available on FTD cases lacking mutations in the known genes.
- Spanish CATFI (Catalan Frontotemporal Initiative; 3 Spanish sites, co-PI Sanchez-Valle): comprehensive longitudinal collection of clinical, cognitive, neuroimage and biological samples (DNA, plasma, CSF) of > 150 non-genetic FTD patients.

4. The International Frontotemporal Dementia Genomics Consortium (IFGC). The IFGC collects DNA samples from across the world, with an emphasis on European countries. Samples from Australia, Belgium, Denmark, France, Germany, Italy, the Netherlands, North America (USA and Canada), Spain, Sweden, and the UK are included. The most recent genetic study (2014) performed with DNA samples from these patients included more than 3,500 FTD patients and additional patient samples have been collected since then. Only DNA is available from these patients.

> *Source: Ferrari et al. Frontotemporal dementia and its subtypes: a genome-wide association study. Lancet Neurol. 2014, 13(7):686-99.*

5. **The International FTLD-TDP WGS Consortium**: Similar to IFGC, this consortium was designed to identify novel genetic risk factors for FTD, but in this specific cohort there is a focus on patients with pathologically confirmed FTD with TDP-43 pathology. DNA and/or brain tissue on more than 500 unrelated FTLD-TDP patients from 23 European, North American and Australian participating sites has already been collected and included in a recent genetic study. Expansion of the cohort and datasets is ongoing. While the consortium was initially led from the US, it is now led from VIB, Belgium as a result of the move of the PI (Rademakers) from the US to Belgium.

> *Source: Pottier et al. Genome-wide analyses as part of the international FTLD-TDP whole-genome sequencing consortium reveals novel disease risk factors and increases support for immune dysfunction in FTLD. Acta Neuropathol. 2019, 137(6):879-899.*

6. **ARTFL/LEFFTDS** (ALLFTD) study. In recognition of the need to advance toward treatment of FTD, the National Institutes of Health (NIH, US) initiated two large studies in 2014: Advancing Research and Treatment in Frontotemporal Lobar Degeneration study (ARTFL) focused on familial and sporadic FTD patients without known gene mutations and the Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects study (LEFFTDS), focused on families with known mutations in the three main autosomal dominant genes, MAPT, GRN and C9orf72. ARTFL was designed to prepare for clinical trials by establishing a network of North American centers (now numbering 18) studying FTD with shared methods and enrolling participants affected by sporadic and familial. The familial cohort in ARTFL includes families with no known mutations to facilitate gene discovery. LEFFTDS was designed to intensively study the natural history of familial FTD in families affected by MAPT, GRN and C9orf72 mutations very similar to the design of GENFI discussed above. The LEFFTDS study uses a subset of eight of the ARTFL sites and conducts at least three annual visits per participant to allow better modeling of change over time, and includes comprehensive clinical/neuropsychological assessment, brain MRI and biofluid collection, including CSF. At the start of both projects, management of these grants was integrated and more than 1,100 participants have now been enrolled in the combined ARTFL/LEFFTDS studies. Importantly, biofluid samples on more than 1,000 individuals are available at the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD), and accessible to European investigator. Just last month, a new 5-year cycle of ARTFL and LEFFTDS commenced, this time as one combined study called ALLFTD. Patient samples including DNA, RNA, plasma, serum, CSF and PBMCs which could be used for the generation of induced pluripotent stem cells (iPSCs), will continue to be available through NCRAD.

7. **The BELNEU FTD cohort.** The Belgian FTD cohort constitutes a collection of 646 Belgian FTD and FTD-ALS patients, collected in the framework of the Belgian Neurology (BELNEU) Consortium, an ongoing multicenter collaboration of 10 neurology departments and memory clinics across Belgium (PIs Van Broeckhoven, van der Zee). At the different centers, approved recruitment programs are implemented for inclusion of research participants. The resulting Belgian FTD cohort represents a well-characterized group of patients, both phenotypically and genetically, in whom for 528 patients the molecular defect remains elusive. Patients undergo neurological examination, neuropsychological testing, biochemical analyses, neuroimaging and regular follow-up. Included patients can be isolated patients, or patients belonging to nuclear or extended families with dementia. A wide range of standardized information is collected including demographic information (gender, date of birth and death, ethnicity, nationality) and medical information (diagnosis, age at onset, age at examination, family history, inheritance mode, MMSE score, follow-up, and eventual cause of death). DNA, RNA, plasma, serum, CSF, brain, lymphocytes and EBV cell lines are systematically collected, and in selected cases fibroblasts and iPSC-derived neurons. When patients come to autopsy, extensive neuropathology is performed. Supplementing this, copies of medical records, cognitive test scores, neuro-imaging reports and files, and neuropathology reports (together with post-mortem brain tissue) are available.

8. **The EU EODC FTD cohort.** The European Early-Onset Dementia Consortium (EU EODC, PI van der Zee), brings together 41 expert research groups across Europe, joining efforts to collect well-documented patient cohorts of rare and understudied early-onset forms of dementia for neurogenetic and clinical research. This multidisciplinary collaboration has led to a unique collection of EOD study populations with long clinical follow-up and patient biomaterials. The EU EOD

Consortium covers the whole realm of translational genetic dementia research, starting at the collection of powerful, well-documented patient cohorts, promoting gene-discovery, to epidemiological characterization of novel dementia genes, investigation of different mutation/disease mechanisms and translation into diagnostic and prognostic relevant genotype-phenotype correlations. The consortium has invested in the systematic collection of biomaterials (DNA, plasma, serum, CSF, brain, lymphocytes, EBV cell lines) of well-documented EOD patients, relatives and control individuals for advanced molecular genetic studies and translational research. Within this EU EOD patient collection, DNA and linked demographic and clinical information has been collected on 2688 FTD patients including 1770 FTD, 96 FTD-ALS and 560 ALS patients without an identified causal mutation.

Sources:
van der Zee et al. A pan-European study of the C9orf72 repeat associated with FTLD: geographic prevalence, genomic instability, and intermediate repeats. Hum Mutat. 2013 Feb;34(2):363-73.
van der Zee et al. Genetic variability in SQSTM1 and risk of early-onset Alzheimer dementia: a European early-onset dementia consortium study. Neurobiol Aging. 2015 May;36(5):2005.e15-22.
Verheijen et al. Common and rare TBK1 variants in early-onset Alzheimer disease in a European cohort. Neurobiol Aging. 2018 Feb;62:245.e1-245.e7.

9. **The GENESIS FTD WES cohort.** Joined aggregations and collaborative shared analysis of >300 whole-exome datasets (WES) of FTD patients with a positive family history, but negative for mutations in all known FTD genes (in particular C9orf72, GRN and MAPT) in the web-based GENESIS NGS software platform, where advanced sharing abilities allow that data analysis does not exclusively happen within the labs of a few PIs, but datasets are rather available immediately to all partners and involved collaborators for joined analyses (PI: Synofzik).

Brain banks

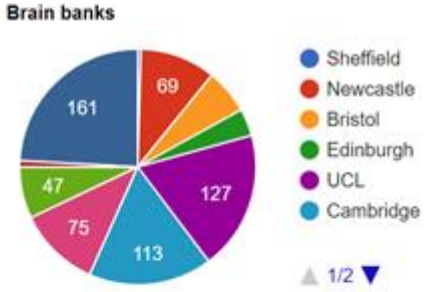
The Netherlands brain bank (NBB) has a total of 9607 FTD samples from 144 independent donors across the FTD spectrum (5895 samples from males, 3712 samples from females). The numbers break down as follows based on pathological(sub)types:

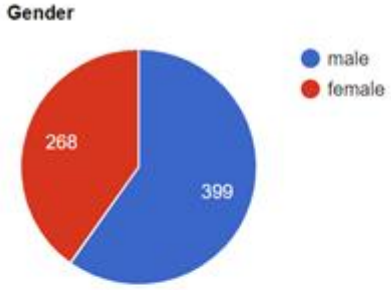
- FTD Pick's disease (= unique tau-pathology): 2314 samples from 35 donors (1685 samples from male donors, 629 from female donors);
- FTD tauopathy: 2440 samples from 41 donors (1282 samples from male donors, 1158 from female donors);
- FTD-TDP type A (progr.): 915 samples from 15 donors (487 samples from male donors, 428 from female donors);
- FTD-TDP type B (C9orf): 1341 samples from 20 donors (557 samples from male donors, 784 from female donors);
- FTD-TDP type C: 797 samples from 11 donors (404 samples from male donors, 393 from female donors);
- FTD-TDP with additional motor neuron disease: 792 samples from 11 donors (656 samples from male donors, 136 from female donors);

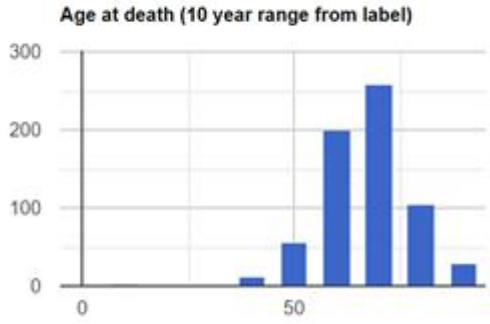
- FTD-FUS: 691 samples from 9 donors (542 samples from male donors, 149 from female donors);
- FTD ubiquitin (unknown disease protein): 148 samples from 2 female donors.

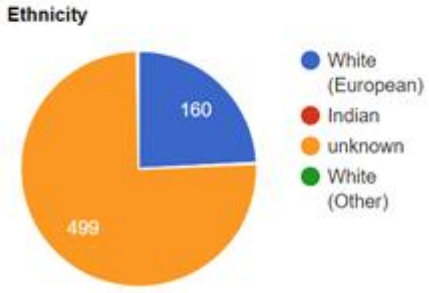
The Brain Bank at Karolinska Institutet (ki.se/brainbank) has a total of 107 independent donors across the FTD spectrum of whom more than 37 have a known genetic disease causing mutation. IN half of the cases there is frozen tissue available as well as formalin fixed paraffin embedded tissue. The majority of cases has other fluid samples such as DNA, and a minority also plasma, serum, CSF and fibroblasts.

The UK Brain Banks collectively hold samples from 667 donors with a pathological diagnosis of FTD:





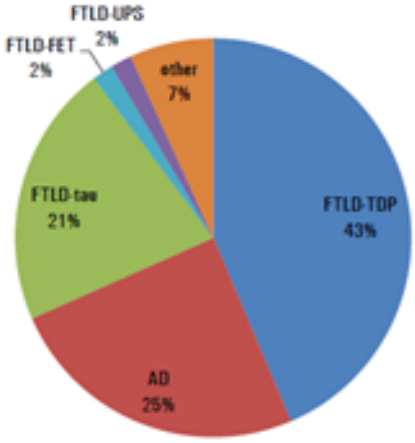




GENFI-BrainNet is a collaboration between a number of brain banks connected to the Genetic FTD Initiative cohort study. It links the Queen Square Brain Bank (UCL, UK) and the Netherlands Brain Bank with brain banks in Cambridge and Manchester (UK), Milan (Italy), Karolinska Institute (Sweden), Barcelona and San Sebastian (Spain), Tubingen and Munich (Germany), Leuven (Belgium) and Toronto and Quebec (in Canada). Brain tissue from 300 people with genetic forms of FTD is available.

Number	Centre	Country	Brain Bank	Send to	Contact	C9orf72				GRN			
						TDP A	TDP B	MND	Unclass	TDP A	TBK1	MAPT	TOTAL
1	UCL London	UK	Yes		Tammaryn Lashley	9	2	0	0	16	1	17	45
2	Cambridge	UK	Yes		Kieren Allinson	6	6	0	0	0	0	6	18
3	Brescia FBF	Italy	No	Milano INCB									
4	Brescia UNIBS	Italy	No	Milano INCB									
5	Milano UNIMI	Italy	No	Milano INCB									
6	Milano INCB	Italy	Yes		Giorgio Giaccone	1	1	1	0	3	0	4	10
7	Toronto	Canada	Yes		Julia Keith	0	0	0	2	7	0	0	9
8	London Ontario	Canada	No	Toronto or Quebec									
9	Rotterdam	Netherlands	Yes		J M Rozemuller	0	11	0	17	12	0	26	66
10	Firenze	Italy	No	Milano INCB									
11	Oxford	UK	Yes		Olaf Ansorge	12	0	0	0	3	0	0	15
12	Stockholm	Sweden	Yes		Inger Nennesmo	8	2	3	7	6	4	4	34
13	Manchester	UK	Yes		Federico Roncaroli	9	5	4	0	12	0	11	41
14	Quebec	Canada	Yes		Stephan Saikali	0	0	0	0	0	0	4	4
15	Barcelona	Spain	Yes		Ellen Gelpi	0	10	0	10	3	0	9	32
16	Lisboa	Portugal	No	Coimbra									
17	San Sebastian	Spain	Yes		Maria Caballero Martinez	0	0	0	0	7	0	0	7
18	Tubingen	Germany	Yes		Manuela Neumann	0	8	0	0	2	0	1	11
19	Leuven	Belgium	Yes		Dietmar Rudolf Thal	0	2	0	0	2	0	0	4
20	Montreal	Canada	Yes	Quebec									
21	Paris	France	No	Lille									
22	Munich	Germany	Yes		Armin Giese								
23	Ulm	Germany	No	Munich									
27	Coimbra	Portugal	Yes		Ricardo Taipa	0	0	0	0	1	0	0	1
						45	47	8	36	74	5	82	297

The Antwerp IBB Brain Bank. The Brain Bank of the Institute Born Bunge (IBB BB) holds donated brain samples on over 6000 patients. These include brains from over 110 patients within the clinical FTD spectrum with full neuropathological characterisation. The graph below illustrates the distribution of postmortem neuropathological diagnosis of suspected FTD patients in the IBB Biobank.



The EU EODC FTD cohort holds biomaterials, clinical and pathological characterisation, and genetic profiling on 111 pathology-confirmed FTLD cases.

The Barcelona Hospital Clínic-IDIBAPS Neurological Tissue Bank currently has 2,000 brains and spinal cords covering a wide range of neurodegenerative diseases, including approx 100 cases with FTLD.

c. AVAILABLE OR POTENTIAL NEW PRECLINICAL MODELS (CELLS AND TISSUES, ORGANOIDS, ANIMALS, HUMAN *IN VIVO* DISEASE MODELS)

Models of human disease, whether a yeast, nematode, fruit fly, mouse, grafted animals, non-human primates, cultured cells or organoids, allow us to investigate the underlying biology of disease, while also being useful to screen drugs in preclinical studies for the development of disease modifying therapeutics. Models of FTD have been created based on identified gene mutations. The mutation-based models have provided remarkable insights on the pathogenesis of FTD proteinopathies and are used to screen potential therapeutics that can be assessed for efficacy via pathology, molecular, biochemical or behavioral assays. However, as with other neurodegenerative diseases, none of the currently available models fully captures the pathology, behavior and biochemical signature of FTD. Below is a selection of the currently available models used in the field.

Animal Models of FTD

Transgenic mice. There are several transgenic mice modelling different forms of FTD with models focusing on tau, TDP-43, progranulin, FUS, VCP, CHMP2B and C9ORF72. The clinical presentation of FTD patients includes a wide range of functional changes, with behavioural, memory, language, eating/metabolic, and motor deficits, in addition to variable neuropathology. Mice models recapitulate some of the clinical presentation of FTD patients. For instance, GRN knockout mice display impaired fear conditioning and remain immobile for longer periods in the forced swim test, which may relate to a depressive-like state. Other phenotypic features such as repetitive behaviour are observed in FTD models. As an example, repetitive grooming has been reported in aged mutant tau-transgenic mice where it increases with age, and is hypothesized to reflect ventral striatum dysfunction.

Sources:
Filiano et al. Dissociation of frontotemporal dementia-related deficits and neuroinflammation in progranulin haploinsufficient mice. J Neurosci. 2013 Mar 20;33(12):5352-61.
Solomon et al. Review: Modelling the pathology and behaviour of frontotemporal dementia. Neuropathol Appl Neurobiol. 2019 Feb;45(1):58-80.
Warmus et al. Tau-mediated NMDA receptor impairment underlies dysfunction of a selectively vulnerable network in a mouse model of frontotemporal dementia. J Neurosci. 2014 Dec 3;34(49):16482-95.
Yin et al. Behavioral deficits and progressive neuropathology in progranulin-deficient mice: a mouse model of frontotemporal dementia. FASEB J. 2010 Dec;24(12):4639-47.

In terms of pathology observed in diseased brains, mouse models of FTD show disease-specific changes including nuclear clearing of endogenous TDP-43, cytoplasmic mislocalization, phosphorylation, and ubiquitination of aggregated TDP-43 accompanied by neuronal death. However the full-blown TDP43 pathology observed in patients is only mildly present in mouse models. For instance, it has been challenging to even show a TDP-43 pathology in C9ORF72 mouse models. An AAV mouse model expressing (G4C2)66 was shown to harbour TDP-43 pathology, yet it has been unclear how the quantities of the repeat expansion expressed in the model relate to the quantities found in human C9FTD patients.

Source: Chew et al. Neurodegeneration. C9ORF72 repeat expansions in mice cause TDP-43 pathology, neuronal loss, and behavioral deficits. Science. 2015 Jun 5;348(6239):1151-4.

Importantly, even though animal models recapitulate part of the disease mechanism, they also can highlight cellular level differences. For instance, a transcriptomic study of GRN KO mice revealed an age-dependant upregulation of lysosomal and innate immunity genes in microglia. The work by Huang's group shed light on the cell specific vulnerability and suggested that microglia activation is a major driver of neurodegeneration.

Source: Lui et al. Progranulin Deficiency Promotes Circuit-Specific Synaptic Pruning by Microglia via Complement Activation. Cell. 2016 May 5;165(4):921-35.

While the human disease is highly complex, studies on mouse models tend to focus on specific phenotypes reducing disease complexity and allowing exploration of underlying mechanisms. Combinations of models may then be used to 'rebuild' the complexity of the human disease and eventually elucidate FTD in its entirety.

Source: Mouse models of frontotemporal dementia: A comparison of phenotypes with clinical symptomatology. Neurosci Biobehav Rev. 2017 Mar;74(Pt A):126-138.

Caenorhabditis elegans (*C.elegans*) is a nematode with a simple nervous system, short reproductive life cycle and span, and a sequenced genome that has gained immense popularity as a model system in biology. Furthermore, the complete neuronal lineage and synapses being known, complemented by a high degree of conservation with human genome, has made this model a proven powerhouse in neuroscience research and often providing the leading edge in understanding the molecular biology of neuronal degeneration. Currently, C. elegans models are available for GRN, C9ORF72 and MAPT. Although these models are relevant and useful to investigate disease pathology, similarly to other models, they do not fully replicate the features of human disease. For example, as reported by Pir et al, the detergent-insoluble tau aggregates observed in human tauopathy brains are not observed in the C. elegans MAPT model.

Sources:
Butler et al. Age- and stress-associated C. elegans granulins impair lysosomal function and induce a compensatory HLH-30/TFEB transcriptional response. PLoS Genet. 2019 Aug 9;15(8):e1008295.
Corrionero and Horvitz. A C9orf72 ALS/FTD Ortholog Acts in Endolysosomal Degradation and Lysosomal Homeostasis. Curr Biol. 2018 May 21;28(10):1522-1535.e5.
Pir et al. Caenorhabditis elegans models of tauopathy. FASEB J. 2017 Dec;31(12):5137-5148.

Drosophila. *Drosophila melanogaster* (the common fruit fly) models have proven an excellent route to study the toxicity of FTD proteinopathies. Drosophila models are available for the following FTD genes: MAPT, C9ORF72, CHMP2B, VCP, FUS, TARDBP. However, there are currently no models for PGRN, TBK1, and the genetic modifier TMEM106B (see table below). Flies transfected with human wild type and mutant tau proteins conveniently show degenerative changes in their retinas, as well as having locomotor dysfunction and shortened lifespans. The C9ORF72 model has shown that a toxic dipeptide repeat secondary structure is not necessary to cause neurodegeneration in adult flies; instead, the aberrant translation of RNA is sufficient. The fruit fly has also proven to be a practical

model for high throughput screening. For instance, drosophila models of MAPT have successfully identified various Tau-induced neurodegeneration modifiers, including eight Tau toxicity suppressors and 16 enhancers.

Table 1. Classification of FTD-associated loci.

Gene Name	C9ORF72	MAPT	CHMP2B	FUS	VCP	TARDBP (TDP-43)	PGRN	TBK1	TMEM106B
Full Name	Chromosome 9 open reading frame 72	Microtubule—associated protein tau	Chromatin modifying protein 2B	Fused in sarcoma	Valosin containing protein	Transactive DNA-binding protein	Progranulin	TANK-binding kinase 1	Transmembrane protein 106B
Location	9p21.2	17q21.32	3p11.2	16q11.22	9p13.3	1p36.22	17q21.32	12q14.2	7q21.3
Incidence Rate	25%	Familial: 10–20% Sporadic: 0–3%	Rare	Rare	1.6%	Rare (<20 cases)	Familial: 5–20% Sporadic: 1–5%	1.1%	Unknown
Normal Function	• role in autophagy • part of a complex that serves as a GDP-GTP exchange factor for RAB8a and RAB39b	• stabilization of microtubules • promotion of microtubule tubulin binding	• necessary for transport in endosomal sorting complex (ESCRT-III)	• involved in RNA processing and DNA repair	• transcriptional activation • apoptosis • protein degradation • membrane fusion	• RNA metabolism regulator	• growth factor for neurons and other cells	• engages in various cell signaling pathways, including immune response, cell proliferation and growth	• regulation of protein trafficking, lysosome size, and lysosome motility
Deficits Caused	• lysosome accumulation • abnormal microglia immune response	• disruption of normal tau binding to tubulin causing hyperphosphorylated tau build up	• build up of vesicular structures and autophagosome • neuronal cell loss, and dendritic retraction	• reduction of dendrite arborization in spinal neurons	• disruption of autophagy • protein degradation by ubiquitin-proteasome	• increases B-cell lymphoma 2 (Bcl-2) mediated apoptosis caused by improper regulation of calcium signaling	• low PGRN levels and accumulation of truncated granulin domain cause haploinsufficiency	• unknown method of pathogenicity	• causes lysosome enlargement • impaired endo-lysosome degradation
Drosophila Model	Yes [13]	Yes [22]	Yes [41, 81, 84–86]	Yes [32]	Yes [34]	Yes [32]	No	No	No
Drosophila Homolog	None	tau/ CG45110	CG4618	cir	*ter94*	*TBPH*	N/A	N/A	N/A

Sources:
Mizielinska et al. C9orf72 repeat expansions cause neurodegeneration in Drosophila through arginine-rich proteins. Science. 2014 Sep 5;345(6201):1192-1194.
Schulman and Feany. Genetic modifiers of tauopathy in Drosophila. Genetics. 2003 Nov;165(3):1233-42.
Vandal et al. Molecular Genetics of Frontotemporal Dementia Elucidated by Drosophila Models-Defects in Endosomal-Lysosomal Pathway. Int J Mol Sci. 2018 Jun 9;19(6). pii: E1714.

Interestingly, studies to model tauopathies have utilized expression systems to target the over-expression of either mutant or wild type tau to specific neuronal or glial cells in both larvae and adult Drosophila. The consequences of tau expression could then be investigated both by assessing neuronal function and cell loss/toxicity. Collectively, these models have revealed key complex pathogenic mechanisms by which abnormalities in tau cause neurodegeneration. This complexity may reflect the fact that multiple cell types are affected, each having its own cell type autonomous mechanism, further highlighting the relevance and potential impact of in-depth single-cell sequencing experiments.

Source: Sun and Chen. Studying tauopathies in Drosophila: A fruitful model. Exp Neurol. 2015, 274(Pt A):52-7.

Zebrafish (*Danio rerio*). Zebrafishes have been used extensively as neurological disease models to study developmental pathways and gene mutations. Most human genes have a zebrafish homologue, with about 70% homology in protein sequence. Due to the transparency of their embryos, Zebrafish are being increasingly exploited for high throughput drug screening. In particular, Zebrafish have been used to model tauopathies as well as TDP-43 proteinopathies. For instance, several FTD relevant models are available for MAPT, C9ORF72, TDP43. However, so far it has been challenging to obtain a GRN zebrafish model that is FTD relevant. Indeed, a stable GRN loss of function Zebrafish mutant did not have obvious FTD- or neuronal ceroid lipofuscinosis (NCL)-related biochemical and neuropathological phenotypes. Loss of zebrafish GRN might therefore either be fully compensated or only become symptomatic upon additional challenges highlighting a limitation of this model.

Sources:
Ding et al. Tau Protein and Zebrafish Models for Tau-Induced Neurodegeneration. J Alzheimers Dis. 2019;69(2):339-353.
Paquet et al. Transgenic zebrafish as a novel animal model to study tauopathies and other neurodegenerative disorders in vivo. Neurodegener Dis. 2010;7(1-3):99-102.
Philips and Westerfields. Zebrafish models in translational research: tipping the scales toward advancements in human health. Dis Model Mech. 2014, 7(7):739-43.
Solechenberger et al. Granulin knock out zebrafish lack frontotemporal lobar degeneration and neuronal ceroid lipofuscinosis pathology. PLoS One. 2015, 10(3):e0118956.

Cell Models of FTD

Neuronal or glial cell cultures can be useful as an inexpensive model to tease out and study cell-specific biochemical pathways and early discovery proof of concept and drug screening studies. However, these cells are often obtained from rodent brain, which may not recapitulate all aspects of human brain cells. Commercially available human neuronal and glial cell lines are also popular, but are in essence tumor cells. A more pertinent model is the use of human derived cell lines such as Induced Pluripotent Stem Cells (iPSCs).

Induced Pluripotent Stem Cells (iPSCs) from FTD and FTD-ALS Patients

Modeling of neurological diseases has taken a great leap forward with advances in cell culture technology. Adult human tissue cells can be converted to a stem cell-like state with the capacity to differentiate into any kind of cell (pluripotency). Fibroblast cells, conveniently obtained from skin biopsies, are reprogrammed to become iPSCs. Neuronal cells and glial cells can then be induced to develop from these adult stem cells.
FTD gene mutation-specific iPSC lines effectively provide a “disease in a dish” model that allows us to study cell pathways representative of those in specific cell types. Patient-derived neurons from C9ORF72 expansion carrier recapitulated aspects of C9ORF72-associated pathology such as high levels of p62 protein and compromised autophagy. Similarly, motor-neurons with C9ORF72 expansions revealed disruption of the lysosomal pathway, increase in glutamate receptors, and decreased viability. Independently, iPSC-neurons derived from GRN mutation carriers present with a 50% decrease in the levels of both secreted and intracellular GRN protein, recapitulating the haploinsufficiency disease phenotype.

Sources:
Almeida et al. Induced pluripotent stem cell models of progranulin-deficient frontotemporal dementia uncover specific reversible neuronal defects. Cell Rep. 2012 Oct 25;2(4):789-98.
Almeida et al. Modeling key pathological features of frontotemporal dementia with C9ORF72 repeat expansion in iPSC-derived human neurons. Acta Neuropathol. 2013 Sep;126(3):385-99.
Marchetto et al. Induced pluripotent stem cells (iPSCs) and neurological disease modeling: progress and promises. Hum Mol Genet. 2011, 20(R2):R109-15.

The National Institutes of Health (NIH/NINDS) has created disease-specific iPSC consortia to facilitate research in FTD, ALS, PD and Huntington’s disease, and for each of these diseases, including FTD patients with and without known mutations, peripheral blood mononuclear cells (PBMCs) are available. Recently, NCRAD even started with the banking and distribution of iPSCs, which will be available for a fee to researchers across the globe, including Europe. These cells have the potential

to be valuable disease models as well as a drug-screening tool that might answer questions about new drug efficacy in humans, at a preclinical test level.

Organoid models of FTD

So far, conventional experimental animal models, as the ones described above, have proven to be critical to elucidate the role of individual mutated genes in brain development and dysfunction. However, such models also have important limitations that arise from the inherent differences in the development, architecture and function of their brains compared to humans. Similarly, the biggest challenge of using iPSC technology to model human brain is to faithfully and reproducibly generate authentic cell types and to mimic the cell–cell interactions and circuit connectivity of the human CNS. Together, these factors highlight the need for integrating the current experimental models with new in vitro systems that can incorporate patient-derived iPSCs, and that can be used for detailed molecular and functional analysis of living human tissue. Thus, the field of in vitro 3D tissue models such as organoids and spheroids is rapidly expanding.

Source: Quadrato et al. The promises and challenges of human brain organoids as models of neuropsychiatric disease. Nat Med. 2016, 22(11):1220-1228.

Organoid formation closely recapitulates the developmental morphogenic processes occurring in the human body, relying heavily on the self-organizing capacity of mammalian stem cells. By allowing cells to complete entire organogenesis programs in vitro and to recreate their endogenous niches, organoids achieve a close resemblance to human organs in terms of 3D organization and physiology. Such models, have already been shown to recapitulate broad features of the developing brain, such as radial organization of cell types around ventricles and have a proven potential for elucidating the mechanisms underlying neurodevelopmental disorders such as microcephaly.

Sources:
Lancaster et al. Cerebral organoids model human brain development and microcephaly. Nature. 2013, 501(7467):373-9.
Paşca. Building three-dimensional human brain organoids. Nat Neurosci. 2018. doi: 10.1038/s41593-018-0107-3.

The iPSC-disease modeling strategy, generating mini-brains from individuals with neurological disorders, represents a novel and powerful strategy in FTD research and treatment. For example, forebrain organoids generated from human iPSCs derived from a MAPT-P301L mutation carrier FTD patient, exhibited increased levels of p25. In this system, introducing a CRISPR-Cas9-mediated mutation in p35 that inhibits the conversion into p25 resulted in lower levels of total tau and phosphorylated tau in 2-month-old organoids. Increased synaptophysin was also observed, suggesting that inhibiting p25 generation favors synapse formation.
Such models, with a high degree of complexity, combined with the powerful single cell approaches will further our understanding of the etiology of the disease.

Source: Seo et al. Inhibition of p25/Cdk5 Attenuates Tauopathy in Mouse and iPSC Models of Frontotemporal Dementia. J Neurosci. 2017, 37(41):9917-9924

Tissues

Human brain tissue is critical to FTD research, as there currently is no animal or in vitro model that accurately and fully represents the molecular, cellular and anatomical complexity of the human brain. From a clinical perspective, accurate diagnosis can only be definitively confirmed by neuropathological assessment of post-mortem brain tissue. Several specialized brain banks exist (see section c above) which distribute high-quality fixed and frozen brain tissue samples essential for FTD research. Access to such tissues is a great opportunity to assess disease related changes at the bulk and cellular level. Indeed combining highly characterized human brain tissues with single cell approaches such as scRNAseq, scDNAseq, and single cell epigenetic approaches will increase our current understanding of cell specificities in a disease context. However, data collected from these tissues needs to be interpreted with caution since they are collected at an end-stage of the disease.

d. CLINICAL FEASIBILITY

i) Expected clinical time course that allows application and assessment of novel therapeutic strategies

It is likely that 5 – 10 years will be required to apply and assess novel therapeutic strategies.

ii) availability of well-annotated clinical data

Yes X

Within the context of the patient cohorts mentioned above (see section c), clinical data is available including demographics, symptomatology, and physical examination. The FTD Prevention Initiative (FPI) is currently developing a minimum shared dataset across all worldwide genetic FTD studies

iii) possibility for longitudinal sampling of patient samples including liquid or tissue biopsies (preferably in the context of trials promoted by academia or by industrial partners allowing the access to samples)

Yes X

Blood and CSF samples are collected within the patient cohorts mentioned above (see section c). For example in GENFI there are >2,500 participant visits from the 1,000 participants with blood samples taken in virtually all of these visits. Longitudinal samples and data are also available from ALLFTD through the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) and the DZNE FTD DESCRIBE cohort.

e. ETHICAL CONSIDERATIONS (GUIDELINES TO PROTECT PATIENTS PARTICIPATING IN THE RESEARCH)

i) Absence or reduced level of risk during sampling

Blood sampling is very low risk whilst CSF sampling is low risk.

ii) Potential of excluding of subpopulations based on origin, sex, or age (due to existing cohorts etc.)

It is unlikely that subpopulations are excluded due to origin or sex within Europe, although It is recognised that the majority of FTD collaborative research involves the larger Western European countries (see section c)

It has also been recognised that FTD is as common in older ages (70s, 80s) as in younger ages (50s, 60s) although many current cohorts are focused on younger dementias.

f. SEX-RELATED ASPECTS (EXPERIMENTAL DESIGN, ORIGINS OF DISEASE MODELS, DISEASE INCIDENCE, THERAPY RESPONSE, BIAS IN PHYSICIAN TREATMENT)

No clear sex differences in prevalence/incidence of FTD, or life expectancy of FTD patients have been reported.

g. ALIGNMENT WITH NATIONAL/EU STRATEGIES FOR DISEASE RESEARCH PROGRAMMES

The European Reference Network on Rare Neurological Diseases (ERN-RND) aims to address the unmet needs of more than 500,000 people living with RNDs (including FTD) in Europe. The ERN-RND has been established by the EU to support patients and families affected by RNDs which requires much specialised knowledge, treatment and resources. FTD forms one of the disease groups within the ERN-RND (PIs: Le Ber, Vandenberghe, Otto, Rohrer, van Swieten, Synofzik) and has initiated a plan to improve diagnostics and care pathways across Europe for FTD.

Together with other ERNs, the ERN-RND designed and initiated the large EU-funded SOLVE-RD network (2018-2022, budget €15.3 million, coordinator Eberhard Karls Universitaet Tuebingen), with the aim to unravel the molecular diagnosis in molecularly undiagnosed diseases, leveraging the latest advanced genomics techniques and exploiting multi-omics approaches and tissues. FTD is one of the main target diseases of the ERN-RND group within SOLVE-RD, focusing on systematic Whole Exome Sequencing (WES) re-analysis, advanced Whole Genome Sequence analysis and study of somatic mutations in brain-blood DNA pairs by deep-sequencing WES (Co-PIs: Synofzik, Rademakers).

The FTD Prevention Initiative (FPI) brings together research consortia across Europe (including GENFI, see section c), North America (including members of the ARTFL and LEFFTDS consortia) and Australia (Australian Dominantly Inherited Non-Alzheimer Dementias (DINAD) study), as well as other interested parties, to further research into genetic FTD. The FPI currently has a number of ongoing projects, among which are the development of a minimum shared dataset across all worldwide genetic FTD studies, and an investigation of the relationship of age at onset in an individual with genetic FTD to the age at onset within the parents and wider family.

In addition to these European initiatives, 23 European countries have a national dementia and/or neurodegenerative diseases strategy (see the figure and table below) that address, to different degrees, the action areas set by the World Health Organization in the "Global action plan on the public health response to dementia 2017 - 2025", in terms of:

- Dementia as a public health priority;
- Dementia awareness and friendliness;
- Dementia risk reduction;
- Dementia diagnosis, treatment, care and support;
- Support for dementia carers;
- Information systems for dementia;
- Dementia research and innovation.

Among the countries that do not yet have such a strategy in place, Germany is committed to develop such a strategy to be approved beginning of 2020. Portugal, Romania and Slovakia have indicated that they are developing a dementia strategy, and the other countries have acknowledged the need for such a strategy.

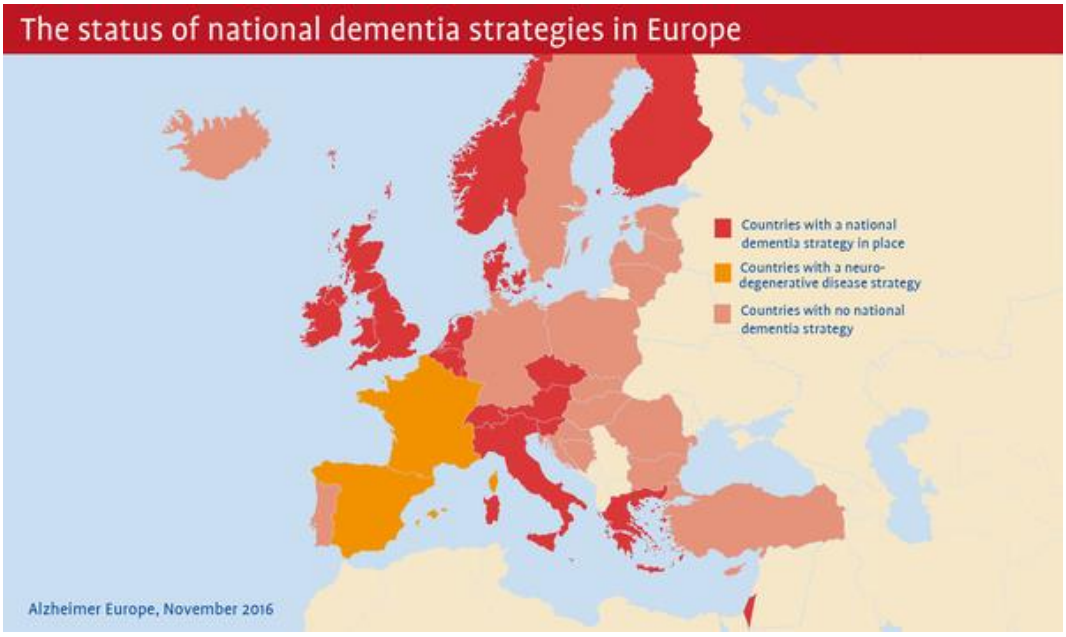


Table 1: Position of countries in relation to a National Dementia Strategy

Countries with a dementia-specific strategy			
Austria	Greece	Netherlands	UK, Northern Ireland
Belgium (Flanders)	Ireland	Norway	UK, Scotland
Cyprus	Israel	Portugal	UK, Wales
Czech Republic	Italy	Slovenia	
Denmark	Luxembourg	Switzerland	
Finland	Malta	UK, England	
Countries with a neurodegenerative diseases strategy			
France	Spain		
Countries with no strategy			
Albania	Germany[3]	Macedonia	Slovakia
Bosnia and Herzegovina	Hungary	Monaco	Sweden[4]
Bulgaria	Iceland	Montenegro	Turkey
Croatia	Latvia	Poland	
Estonia	Lithuania	Romania	

Sources: Alzheimer Europe, 2018, Dementia in Europe in Europe Yearbook 2018: Comparison of National Dementia Strategies. Alzheimer Europe, 2016; A snapshot of the status of National Dementia Strategies around Europe.